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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/754,733	01/08/2004	Pieter de Haan	O 1997.273 US C4	1196

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EXAMINER	
ROYDS, LESLIE A	

ART UNIT	PAPER NUMBER
1614	

DATE MAILED: 02/09/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/754,733	HAAN ET AL.	
	Examiner	Art Unit	
	Leslie A. Royds	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 November 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *13-20* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *13-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☒ Certified copies of the priority documents have been received in Application No. 09/403,139.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 13-20 are presented for examination.

Applicant's Amendment filed October 3, 2005 was received and entered into the application, but was found to be non-compliant. Notice to that effect was sent November 4, 2005. Applicant's Amendment filed November 14, 2005 in response to the Notice was received and entered into the application. Applicant's subsequent submission of the Amendment filed November 28, 2005 was also received and entered into the application and supercedes the Amendment filed November 14, 2005. Accordingly, the specification at pages 1-2 has been amended.

In light of the amendments and accompanying remarks, the objection to the specification for improper incorporation by reference and the objections to the specification for minor informalities as set forth at pages 2-3 of the previous Office Action dated April 1, 2005 have each been hereby **withdrawn**.

In light of the acceptable nature of the Terminal Disclaimers filed October 4, 2005, each of which has been received and entered into the present application, the provisional obviousness-type double patenting rejections and the non-provisional obviousness-type double patenting rejections have each been hereby **withdrawn**.

Objection to the Specification

Applicant has noted that the specification will be amended in reference to the trademark LIVIAL prior to issuance of this application. Insofar as the specification has not been amended to properly set forth the trademarked name, the objection remains proper and is repeated below.

The use of the trademark LIVIAL has been noted in this application at page 1, line 10 of the disclosure. Each letter should be capitalized and be accompanied by the generic terminology wherever the name appears. Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner that might adversely affect their validity as trademarks.

Claim Rejection - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 13-20 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Kelder et al. (U.S. Patent No. 4,701,450; 1987) in view of Stedman's Medical Dictionary (1972; p.589), Handbook of Pharmaceutical Excipients (1986, p.108-110, 259-260, 289-293), Loliger et al.

(U.S. Patent No. 5,364,886; 1994) and Sas et al. (EP 0389035; 1990), each already of record, for the reasons already made of record at pages 3-10 of the previous Office Action dated April 1, 2005.

Applicant's remarks have each been carefully considered, but fail to be persuasive in establishing error in the propriety of the present rejection.

Applicant states that the Examiner has used impermissible hindsight in an attempt to reconstruct the invention from the prior art. Applicant submits that there is nothing in the teachings of the cited prior art that address the question of improved stability and/or storage, nor do any of the cited documents, either alone or in combination, teach or suggest the dosage unit of the present application with a carrier having at least 10% to 40% by weight of starch and wherein the dosage unit is maintained in an atmosphere of 50% to 75% relative humidity until administration. Applicant states that the improved stability of the presently claimed product is made possible only when humid conditions are carefully maintained and submits that without a controlling system that maintains a near overall constant level of relative humidity with small changes in atmospheric pressure, the conditions may vary between a humid atmosphere and a dry atmosphere. Applicant states that Handbook of Pharmaceutical Excipients and Loliger et al. do not remedy the deficiencies of Kelder et al. Applicant states that one looking to the question of stability and/or storage would not be led to the cited prior art to solve the problems with regard to stability and/or storage.

In response to Applicant's argument that the Examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so

long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from Applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). Insofar as the present conclusion of obviousness has been made solely on the knowledge that was generally available to one of ordinary skill in the art at the time of the invention, and not, in any way, from the guidance or direction proposed by Applicant in the present specification, the rejection is proper and has not been constructed via impermissible hindsight.

In response to Applicant's argument that there is nothing in the teachings of the cited prior art that addresses the question of improved stability and/or storage, Applicant's attention is directed to pages 9-10 of the previous Office Action dated April 1, 2005. Crystalline tibolone formulated in combination with starch, ascorbyl palmitate, magnesium stearate and lactose was known to be chemically appreciably more stable than compositions comprising polymorphous tibolone (see Sas, page 1, lines 42-44 and Example 6, page 3, lines 35-52). Such a teaching raises the reasonable expectation of success that the tibolone composition disclosed by Kelder et al., which is also in combination with starch and does not preclude the use of a crystalline form of tibolone, would also have been chemically appreciably more stable, i.e., have increased stability.

In addition, the Handbook reference explicitly acknowledges that uncooked dry starch is quite stable during storage if protected from high humidity and also teaches that starch is commonly used as a diluent or binder in the preparation of potent drugs, particularly dry-filled capsules and tablets (see page 293). Such teachings are reasonably suggestive that the use of

starch in a pharmaceutical preparation would have necessarily imparted stability to the composition since the starch itself was known to be highly stable when protected from high humidity. Furthermore, the reasonable suggestion of increased stability of a pharmaceutical preparation would have also indicated to one of ordinary skill in the art that prolonged storage time may be achieved with a more stable composition because the product could be maintained for longer without significant degradation and, thus, could be stored for an extended period of time.

Furthermore, in response to Applicant's remark that none of the cited references, either alone or in combination, teach or suggest a dosage unit with a carrier having at least 10% to 40% by weight of starch and wherein the dosage unit is maintained in an atmosphere of 50-75% relative humidity until administration, Applicant's attention is directed to pages 4-10 of the previous Office Action dated April 1, 2005. Applicant has presently argued against and discussed the references individually without clearly addressing the combined teachings. It must be remembered that the references are relied upon in combination and are not meant to be considered separately as in a vacuum. Rather, it is the combination of all of the cited and relied upon references that make up the state of the art with regard to the claimed invention. Applicant's claimed invention fails to patentably distinguish over the state of the art represented by the cited references and the scientific reasoning that would have been generally used by one of ordinary skill in the art. See *In re Young*, 403 F.2d 754, 159 USPQ 725 (CCPA 1968) and *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981).

In the instant case, it is again noted that while the embodiment of Example 1 (see Kelder et al., col.4, lines 49-68) that was relied upon for the present rejection does not explicitly teach

the exact range of components as presently claimed, Kelder et al. teaches a particular embodiment of the disclosed composition in which the active compound, in this case, tibolone (see col.4, lines 49-50 and also col.2, lines 47-49), comprises 2.5 mg of the dose unit in combination with potato starch (10.0 mg), magnesium stearate (0.5 mg), ascorbyl palmitate (0.2 mg), amylopectin (2.0 mg) and lactose, in an amount to make up to 100 mg of the tablet. Thus, for a 100 mg tablet as disclosed in line 54 of Kelder et al., tibolone is 2.5%, potato starch is 10%, magnesium stearate is 0.5%, ascorbyl palmitate is 0.2%, amylopectin is 2.0% and lactose is 84.8% of the final tablet product. Thus, such a formulation is sufficient disclosure or a reasonable suggestion to one of ordinary skill in the art that the proportions exemplified could have been modified to determine the most optimal and workable amounts of the claimed components.

In further support thereof, Applicant is again directed to the MPEP at §2123, which states, "A reference may be relied upon for all that it would have reasonably suggested to one having ordinary skill in the art, including non-preferred embodiments...Disclosed examples and preferred embodiments do not constitute a teaching away from a broader disclosure or non-preferred embodiments."

While Applicant remarks that the improved stability of the presently claimed product is made possible only when humid conditions are carefully maintained and submits that without a controlling system that maintains a near overall constant level of relative humidity with small changes in atmospheric pressure, the conditions may vary between a humid atmosphere and a dry atmosphere, have been carefully considered, such does not change the fact that the cited prior art does not preclude storage conditions in which relative humidity would be at or between 50%

and 75%. As previously stated, the present claims merely state that the dosage unit must be "*contained*" in a humid atmosphere until administration, and does not expressly state the length of time or the particular conditions (i.e., temperature and pressure) that are intended from the present claims. Thus, because relative humidity fluctuates as the atmospheric temperature and pressure change, such conditions of relative humidity would have been reasonably expected to occur at any storage temperature, ambient or not, depending on the atmospheric pressure. Absent factual evidence to the contrary, such conditions are not considered to be outside the scope of the reference.

Furthermore, it is noted that Applicant has merely claimed that the composition is "contained" in a humid atmosphere of 50-75% relative humidity. Taken in its broadest reasonable interpretation, the fact that the composition is "contained" in a humid atmosphere is not reasonably indicative of the length of time the composition is intended to be kept in such humidity. Thus, the mere fact that the composition may have been, at any one point in time, kept in an atmosphere of 50-75% relative humidity, such conditions would have been reasonably expected from the reference, given that such conditions would have necessarily occurred depending on fluctuations in temperature and pressure, and are considered to meet the limitation of the claim and do not provide any patentable moment to the present claims over what was known from the prior art.

In addition, Applicant is reminded that compositions of matter are based upon their material components and physical form. Thus, the mere fact that Applicant may be intending to contain the composition comprising 0.1-10% tibolone and 10-40% by weight starch in a humid atmosphere of 50-75% amounts to no more than a recitation of the intended use of the

composition and fails to impart any material or physical property to the composition that is not already present in the cited prior art.

Applicant's attention is drawn to the MPEP at §2111.02[R-2], which states, "During examination, statements in the preamble reciting the purpose or intended use of the claimed invention must be evaluated to determine whether the recited purpose or intended use results in a structural difference (or, in the case of process claims, manipulative difference) between the claimed invention and the prior art...***If a prior art structure is capable of performing the intended use as recited in the preamble, then it meets the claim***." (emphasis added)

In response to Applicant's argument that Handbook of Pharmaceutical Excipients or Loliger et al. do not teach the use of 10-40% by weight of starch in the carrier to impart stability or maintaining the dosage unit at 50-75% relative humidity, the test for obviousness is not whether the features of a secondary reference may be bodily incorporated into the structure of the primary reference; nor is it that the claimed invention must be expressly suggested in any one or all of the references. Rather, the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981).

In the instant case, neither the Handbook reference nor the Loliger et al. reference were relied upon to teach, in its entirety, the presently claimed invention. Rather, the references were relied upon to show the knowledge generally available to one of ordinary skill in the art at the time of the invention. Thus, the fact that Handbook of Pharmaceutical Excipients or Loliger et al. do not teach the entire invention is immaterial because the references were not relied upon to comprehensively teach all of the limitations now presently claimed.

Applicant is also reminded that express motivation to combine must not be explicitly stated in the prior art. Please reference MPEP §2145(X), which states, "However, there is no requirement that an "express, written motivation to combine must appear in the prior art references before a finding of obviousness."

Although Applicant argues that one of skill in the art would not be led to the cited prior art to solve problems with regard to stability and/or storage of tibolone compositions, such an assertion is, respectfully, not persuasive. The skilled artisan would necessarily have considered the prior art generally available at the time of the invention regarding known formulations of tibolone and components commonly used as stabilizers, preservatives and carriers of pharmaceutical preparations. Such a person would not have limited their scope of knowledge only to what was known in the prior art regarding stability and storage characteristics. Thus, the cited prior art is properly considered relevant.

This conclusion is supported by the MPEP at §2141.01(a)[R-2], which states, "The Examiner must determine what is 'analogous prior art' for the purpose of analyzing the obviousness of the subject matter at issue. 'In order to rely on a reference as a basis for rejection of an Applicant's invention, the reference must either be in the field of Applicant's endeavor or, if not, then be reasonably pertinent to the particular problem with which the inventor was concerned.' ... '*A reference is reasonably pertinent if, even though it may be in a different field from that of the inventor's endeavor, it is one which, because of the matter with which it deals, logically would have commended itself to an inventor's attention in considering his problem.*" (emphasis added)

For these reasons and those already made of record at pages 3-10 of the previous Office Action dated April 1, 2005, claims 13-20 remain properly rejected.

Conclusion

Rejection of claims 13-20 remains proper and is **maintained**.

No claims of the present application are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Leslie A. Royds whose telephone number is (571)-272-6096. The examiner can normally be reached on Monday-Friday (8:30 AM-5:00 PM).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached on (571)-272-0951. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Leslie A. Royds
Patent Examiner
Art Unit 1614

January 26, 2006

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